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10/511,910	10/20/2004	Kazushi Imai	TAN-345	4544

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EXAMINER	
CHO, DAN SUNG C	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,910	IMAI, KAZUSHI	
	Examiner	Art Unit	
	Dan-Sung C. Cho	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/26/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

SS. 6/12

DETAILED ACTION

1. This action is in response to the papers filed 3/26/2007. Currently, claims 1-4 are pending. Applicant amended claims 1-4 in the paper dated 3/26/2007.

All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied as necessitated by the amendment. They constitute the complete set being presently applied to the instant Application.

All previous rejections are withdrawn. Response to Applicant's arguments follows. This action is **FINAL.**

New rejections necessitated by the amendment

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of distinguishing rheumatoid arthritis (RA) from osteoarthritis (OA) by detecting upregulation of WNT10B or by detecting, in parallel to WNT10B and inhibition of FRP1 mRNAs expression in synovial fluid and synovial tissue. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches synovium can be used to detect specific mRNAs using RT-PCR technique. Synovium contains a unique population of synovial lining cells in RA and OA that appear to be activated in Wnt signaling phenotypes (Nakamura et al., 2005, American Journal of Pathology, 167:97-105, page 97, right column, paragraph 2). In addition, compared with normal tissues, real-time PCR revealed that mRNA levels of Wnt10b in OA cartilage and RA synovium and FRZB, an FRP, in OA synovium and RA cartilage were significantly down-regulated compared to normal tissues. The levels of Wnt-10b and FRZB (FRP) between OA and RA cartilage and synovium do not appear to significantly change (Nakamura, page 99, Figure 1 and page 102, right column, paragraph 1). Sen et al. also teaches that OA and RA synovium tissue samples have similar WNT10b and Fz 2, 3, 5-7 (Sen et al., 2000, PNAS, 97: 2791-2796; Table 1).

NCBI teaches that, when probed with 1019_g_at probe, the levels of OA and RA samples have a trend of higher WNT10b expression in synovial tissue samples compared to normal samples (NCBI, GDS2126/1018_at and 1019_g_at /WNT10B/Homo sapiens, page 2 graph), whereas when another probe is used for expression analysis of WNT10b, there is no correlation between the expression levels and disease state (page 1). Therefore the same gene expression appears different depending on which probe is used to determine the WNT10B expression levels and does not appear to allow for predictable methods to distinguish between RA and OA.

Guidance in the Specification.

The specification provides no evidence that the upregulation of WNT10B expression in synovial fluid, synovial tissue and concurrent down regulation in FRP1 can be used to distinguish RA from OA. The specification merely discloses of RT-PCR comparisons in 5 RA and 4 OA tissues and is silent with regard to RA is normal tissues. Therefore, the skilled artisan would be unable to predictably determine what constitutes, given the guidance in the specification, "upregulation" of expression of WNT10B in claims 1 and 2 is not enabled. The levels of WNT10b and FRP1 in RA are compared to OA in the specification. Table 2 illustrates results for WNT10B and FRPs for (+) presence or (-) absence. This is not upregulation or inhibition. Upregulation would encompass a quantitative change. Figure 1 illustrates expression of 4/5 and 1/4 WNT10B in RA and OA, respectively. It is noted this cannot be construed as overexpression because guideline levels to determine over or under-expressions are not disclosed. It is also noted that the level of one of the OA sample in lane 8 shows the strongest WNT10b expression levels among 5 RA and 4 OA samples (Figure 1). On the other hand, 4/5 RA but 1/4 OA samples gave positive RT-PCR signal for WNT10B and 1/4 OA and 0/5 RA samples resulted in positive signals. Because of lack of guideline

standard, however, it is difficult to determine if the trend is inhibition or down-regulation specific to either RA or OA. It is also noted that for Figure 1, the sample in lane 8, which has the highest WNT10B also has the highest level of FRP1 as well. Therefore, with regard to claim 3, the distinguishing RA form OA with detection of upregulated WNT10B and down-regulation of FRP1 is not predictable (Figure 1 and 2). As the specification states (page 3, line 13), it merely discloses a trend of presence or absence of WNT10B and FRP1 in synovium. Therefore the specification does not provide guidance to detect upregulation of WNT10b and concurrent inhibition of FRP1 mRNA that can be used to distinguish RA from OA. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

The specification has no working examples of distinguishing RA from OA by detecting upregulation of WNT10b and inhibition of FRP1 in synovial fluid, synovial tissue, (Figure 1). Because the specification does not disclose the expression levels of WNT10b and FRP1 that would distinguish RA from OA (RT-PCR levels), it fails to set a standard of how the detection would result in determining whether the sample is from RA or OA. In addition because of the limited number of samples disclosed in the specification where only 5 RA and 4 OA samples were analyzed, the trend between RA and OA cannot be established with certainty. RA sample 4 and OA sample 8 in Table 2 appear to be more closely related to each other from RT-PCR analysis.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied such as comparative

studies of RA and OA of WNT10b, and any FRP1 in joint synoivial fluid, and synoivial tissues and control expression. The skilled artisan would also be required to perform this analysis in a much larger sample size to determine if the expression of WNT10B and FRP1 can predictably distinguish RA from OA. Given the negative and conflicting teachings in the art n this experimentations is replete with unpredictable trial and error analysis.

Searching the specification does not disclose the use of control tissues. A significant number of RA and OA samples from synovium must be compared to determine if WNT10b and FRP1 and their mutants and transcription variants have upregulation and inhibition of expression levels. Because the specification discloses only presence or absences of WNT10b and FRP mRNAs, a large number of samples are needed to be compared to determine what levels of detection encompasses upregulation and inhibition between RA and OA samples. The skilled artisan would be required to perform additional experimentation to determine the level of upregulation. As discussed the results of the analysis are unpredictable and undue.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the Wnt/Fz signaling which may be involved in the etiology of RA or OA is complex and the

specification has provided no definition of upregulation and inhibition of WNT10b and FRP1, respectively, to enable a skilled artisan in the art to make and use the invention and silent about the negative teachings of the art, the specification provides insufficient guidance to overcome the art recognized unpredictability.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for detecting RA by analyzing WNT10B and FRP. Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that Vas-

Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In The Regents of the University of California v. Eli Lilly (43. USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA. . .' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention.

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. With respect to claims 1 and 2 which encompass detection of "at least the upregulation of expression of WNT10B" the current claims encompass a large genus of nucleic acids which comprise any WNT10B, which encompasses all splice variants and mutants. Similarly, with respect to claims 3 and 4 which encompass "inhabitation of expression of FRP1", the current claims encompass a large genus of nucleic acids which comprise any FRP1, which encompasses, FRP1 and splice variants and mutants. The genus includes an enormous number of variants, and combinations for which no written description is provided in the specification. This large genus is not represented in the specification.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, FRP1 and WNT10b alone is insufficient to describe the genus. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one class of this genus, WNT10b and FRP1, is not representative of the variants of the genus and is insufficient to support the claim.

Next, it is determined whether other identifying characteristics have been described that will describe other members of the genus. In the instant case none of the other identifying characteristics have been described. The specification teaches how to detect WNT10b and FRP1. However the specification does not teach whether a detection of any WNT10b and FRP1 can be used to distinguish RA from OA nor provide any relevant identifying characteristics of a representative number of species within the claimed genus to identify mRNAs whose expression levels detected and have different expression levels can be used to distinguish RA from OA.

Conclusion

Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to the arguments

4. The response asserts in the declaration filed under 37 CFR 1.132 sworn by the instant inventor and in the response in page 3 that the information contained in the

disclosure is sufficient to inform those skilled in the art how to make and use the claimed invention.

This argument has been thoroughly reviewed but was not found persuasive.

The response argues that WNT10B, FRP1 and beta-catenin are negatively stained in samples form normal synovium samples in Figure 1. Newly filed Figure 1 appears to show that normal patient samples do not express WNT10b and FRP1 in synovium samples. The declaration does not give any indication of how the procedure was done whereas there must be nexus between any additional experimentation and what is disclosed in the specification. There is no nexus , however, between these additional experiments and what is disclosed in the specification, as the specification is completely silent with regard to RT-PCR analysis, or immuno staining analysis in any normal synovial fluid or synovial tissue or both as is now instantly claimed.

The MPEP specifically sets forth a requirement for nexus between the evidence and the properties of the claimed invention disclosed in the specification. In the instant case, the Figure 1 represents experimentation in samples that was not disclosed in the specification.

As provided by MPEP **2164.05(a)**, the specification must be enabling at the time invention was made. To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the

steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention.

The response in page 4 asserts that Imai et al teaches in a peer-reviewed journal article that WNT10B mRNA expression is predominantly in RA synovium samples. The response argues the post-filing date article in Biochem and Biophys. Res.Comm. demonstrates WNT family members are upregulated in RA synovium.

This argument has been thoroughly reviewed but was not found persuasive.

With regard to the post-filing date article in Biochem and Biophys. Res.Comm article by Imai et al., whose copy was not provided, Imai et al. discloses that WNT10B is positive 5/7 in RA and 2/7 in OA and also in OA samples, particularly where lane 10 shows greater expression, for that OA sample than any of the RA samples. Further as noted in the response, it appears that as many as 6/14 cases for WNT10b were positive expression in OA by immunostaining although it is not clear where this is taught in the article. Further, the MPEP specifically sets forth a requirement for nexus between the evidence and the properties of the claimed invention disclosed in the specification. In the instant case, Imai et al Figure 3 represents experimentation that was not disclosed in the specification.

The response in page 5 asserts that amendment to the claim, reciting "method of distinguishing RA from OA" and deletion of peripheral blood overcomes the enablement rejection.

This argument has been thoroughly reviewed but was not found persuasive.

The amendments still does not make the invention in the claim enabled because the specification does not provide enablement for distinguishing RA from OA. In the absence of what expression levels would be considered upregulation and inhibition of WNT10b and FRP1, respectively, the specification does not provide teachings of how to distinguish RA from OA by detecting upregulation and inhibition of WNT10b and FRP1 mRNA levels.

The response in page 9 asserts that a post filing date article by Uraguchi et al. teaches primer sequences of all the WNT family members and therefore the limitations of WNT10b is adequately supported. The response further asserts that the amendment from FRP to FRP1 is made to overcome the lack of description rejection under 35 U.S.C. 112.

This argument has been thoroughly reviewed but was not found persuasive.

Uraguchi et al. teaches a pair of primers for a WNT10b transcript but no other primers for alternatively spliced variants and mutants. Uraguchi et al. does not provide any FRP1 primers. Therefore Uraguchi et al. does not provide any additional species of primers for the method of detecting any WNT10b and FRP1 for use in a method of distinguishing RA from OA by determining expression levels of WNT10b and FRP1 in

synovium samples. Additionally, as noted above, NCBI teaches that, when probed with 1019_g_at probe, the levels of WNT10b in RA and OA have a trend of higher expression in synovial tissue samples compared to normal samples (NCBI, GDS2126/1018_at and 1019_g_at /WNT10B/Homo sapiens, page 2 graph), whereas when another probe is used for expression analysis of the same WNT10b gene, there is no correlation between the expression levels and disease state and between RA and OA (page 1). Therefore the WNT10b gene expression is different depending on which probe is used to determine which WNT10B expression levels is detected rather than depending on disease states.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dan-Sung C. Cho whose telephone number is (571) 272-9933. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). The Central Fax Number for official correspondence is (571) 273-8300.

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JEHANNE SITTON
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6/8/07